PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RE/PG5029	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/12830	International filing date *(day/month/year)* 13.11.2003	Priority date *(day/month/year)* 15.11.2002
International Patent Classification (IPC) or both national classification and IPC C07K14/18		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13.05.2004	25.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Irion, A Telephone No: +49 89 2399-8174

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/12830

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-41 as originally filed

Claims, Numbers

1-23 filed with telefax on 19.11.2004

Drawings, Sheets

1/28-28/28 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 17,21,22

   because:

   ☒ the said international application, or the said claims Nos. 21,22 (IA) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 17 (N, IS, IA) are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. R asoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4,5,7-11,13,16,20
	No:	Claims	1-3, 6, 12, 14, 15, 18, 19, and 21-23
Inventive step (IS)	Yes:	Claims	10,11
	No:	Claims	1-9,12-16,18-23
Industrial applicability (IA)	Yes:	Claims	1-16,18-20,23
	No:	Claims	

2. Citations and explanations

see separate sheet

Item I

I.1 The amendments filed with telefax of 19.11.2004 do not appear to introduce subject-matter which extends beyond the content of the application as filed (Article 34(2)(b) PCT).

Item III

III.1 With respect to claims 21 and 22

Claims 21 and 22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(I) PCT).

III.2 With respect to claim 17

The subject-matter of claim 17 does not meet the requirements of Article 6 PCT in that said claim refers on the one hand to claims 1-16 and on the other hand to claims 1-19, including claim 17, thereby rendering the subject-matter of claim 17 unclear. Furthermore, claim 17 refers to "any one of the HCV combinations 1 to 19". However, the expression "HCV combinations 1 to 19" does not exist in any of the claims 1-16. Moreover, assuming combinations of the various HCV proteins mentioned in claims 1-16 are meant, the subject-matter of claim 17 refers to an exceedingly high number of possible combinations, thereby rendering the subject-matter of claim 17 unclear.

Item V

V.1 Reference is made to following documents

D1: WO0130812 (CHIRON CORPORATION) 03 May 2001 (2001-05-03)
D2: WO0138360 (CHIRON CORPORATION) 31 May 2001 (2001-05-31)
D3: WO9610997 (APOLLON, INC ET AL.) 18 April 1996 (1996-04-18)
D4: WO9747358 (CHIRON CORPORATION) 27 November 1997 (1997-11-27)
D5: J.P. MOORMAN ET AL.: 'The C-terminal region of hepatitis C core protein is required for Fas-ligand independent apoptosis in Jurkat cells by facilitating Fas oligomerization', VIROLOGY, 01 August 2003 (2003-08-01), vol. 312, pages 320-329

V.2 Novelty (Article 33(2) PCT)

V.2.1 With respect to claims 1-3, 6, 12, 14, 15, 18, 19, and 21-23

Document D2 describes a vaccine against HCV comprising a fusion protein comprising the **specific combination NS3-NS4b-NS5b combined with core**, which might be truncated (p. 26 l. 22 and p. 28 l. 11-14). Expression constructs comprising ΔNS3NS5 and either Core-121, Core-140, Core-150 or Core-173 within one expression cassette are described (p. 54 l. 27 - p. 56 l. 4). "Expression levels of the ΔNS3NS5-Core-173 construct were much less than that of the ΔNS3NS5-Core-121 construct" and D2 states that "there is a correlation of protein expression levels and the length of HCV core" (p. 56 l. 16-18). Furthermore, the constructs comprising Core-140 or Core-150 were expressed at a similar level as the ΔNS3NS5-Core-173 construct (p. 56 l. 20-22). The NS3 protein is encoded by a nucleic acid sequence having an N-terminal deletion to remove the catalytic domain. Said polypeptide comprises a deletion in, or mutation of, the NS3 protease active site region to render the protease non-functional (p. 10 l. 27 - p. 11 l. 7). The polypeptide comprising the proteins before-mentioned and the DNA polynucleotide molecule encoding said polypeptide are described (p. 4 l. 24-31). Gold particles coated with the DNA molecule used for vaccination by gene gun are described (p. 44 l. 17-22). Said DNA may be comprised in a plasmid. A method of eliciting an immune response against HCV using the polynucleotide mentioned above is described (p. 6 l. 23-25). Therefore, the subject-matter of claims 1-3, 6, 12, 14, 15, 18, 19, and 21-23 is not considered novel in the sense of Article 33(2) PCT.

V.2.2 With respect to claims 4, 5, 7-11, 13, 16, and 20

None of the documents cited in the international search report disclose the subject-matter as defined in claims 4, 5, 7-11, 13, 16, and 20. Therefore, said claims are considered novel in the sense of Article 33(2) PCT.

V.3 Inventive step (Article 33(3) PCT)

V.3.1 With respect to claim 4

The subject-matter of claim 4 differs from the closest prior art document D2 in that the core protein is truncated containing only the amino acid residues 1-151. The problem to be solved by the subject-matter of claim 5 may be regarded as to provide a HCV vaccine which is expressed with a high efficiency. Document D3 describes a truncated core protein of HCV consisting of the amino acid residues 1-151 fused to an antigen derived from HBV (p. 12 l. 18-35, p. 15 l. 1-15). Said truncation enhances

the ability of the fusion protein to be secreted, since the C-terminal amino acids of the core protein contain the binding site to the ER, resulting in the retention of the core protein inside the cell cytoplasm. Therefore, the subject-matter of claim 4 is not considered inventive in the sense of Article 33(3) PCT.

V.3.2 With respect to claim 5

The subject-matter of claim 5 differs from the closest prior art document D2 in that the core protein is truncated containing only the amino acid residues 1-165. The problem to be solved by the subject-matter of claim 5 may be regarded as to provide a HCV vaccine which is expressed with a high efficiency. However, the application does not show any experimental evidence that the problem posed is solved by the core protein truncated containing only the amino acid residues 1-165. Therefore, claim 5 is not considered inventive in the sense of Article 33(3) PCT.

V.3.3 With respect to claim 9

The subject-matter of claim 9 differs from the closest prior art document D2 in that more than one expression cassettes encoding the HCV proteins are used instead of a single expression cassette. The technical problem to be solved may be formulated as the provision of an alternative HCV vaccine comprising a polynucleotide encoding core, NS3, NS4B and NS5B. The solution provided in claim 9 resides in the use of more than one expression cassettes. Since the use of more than one expression cassettes instead of only one does not give any surprising effect over D2, the subject-matter of claim 9 is not considered inventive in the sense of Article 33(3) PCT.

V.3.4 With respect to claims 10 and 11

The subject-matter of claims 10 and 11 differs from the closest prior art document D2 in that the expression cassette encoding the Core protein is downstream of the expression cassette which encodes at least one of the other HCV proteins, e.g. the NS5B protein. The technical problem to be solved may be regarded as providing an alternative HCV vaccine. None of the documents cited in the international search report suggests that the position of the polynucleotide encoding the Core protein downstream of the other expression cassette would result in an increased expression level of the other HCV proteins, for which experimental evidence is given in the Example 6 of the application. Therefore, the subject-matter of claims 10 and 11 is considered inventive in the sense of Article 33(3) PCT.

V.3.5 With respect to claim 20

The subject-matter of claim 20 differs from the closest prior art document D2 in that

the HCV proteins used for vaccination are not codon optimised. The technical problem to be solved may be regarded as the provision of a HCV vaccine which is expressed efficiently in the human organism. The person skilled in the art is aware of the fact, that codon pairings are highly nonrandom and differ from organism to organism, resulting in a low translational efficiency. The solution provided in claim 20 resides in the use of codon optimised polynucleotides for the expression of the HCV antigens. However, the skilled person would combine the teaching of document D4, which describes the production of codon optimised expression of HCV proteins (p. 5 l. 29 - p. 10 l. 8, p. 18 l. 8-21, Figures 12 and 13), with D1 to solve the problem of low translational efficiency. Therefore, the subject-matter of claim 20 is not considered inventive in the sense of Article 33(3) PCT.

V.3.6 With respect to claims 7, 8, 13, and 16

The solution proposed in the dependent claims 7, 8, 13, and 16 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons: the subject-matter of said claims appear to be arbitral selections of straightforward possibilities which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed, i.e the provision of an alternative vaccine composition against HCV.

V.4 Industrial applicability (Article 33(4) PCT)

V.4.1 With respect to claims 1-20 and 23

The subject-matter of claims 1-20 and 23 appears to be susceptible of industrial application.

V.4.2 With respect to claims 21 and 22

The subject-matter of claims 21 and 22 is considered to be a method of treatment by therapy of the human or animal body

For the assessment of the present claims 21 and 22 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

V.5 R mark conc rning document D5

The examination report has been based on an assumed valid priority for the present application. Should the priority of the present application not be valid, the above cited document D5 would be relevant with respect to novelty and inventive step (Article 33(2) and (3) PCT).

V.6 Further remark

V.6.1 With respect to claim 2

Claim 2 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem, i.e. the reduction of the inhibitory effect of Core upon the expression of other HCV proteins. The technical features necessary for achieving this result should be added.

Claims (amended 19/11/04)

1. An HCV vaccine comprising a polynucleotide that encodes the polypeptide sequences of the HCV proteins: core, NS3, NS4B and NS5B, for use in medicine, wherein the polynucleotide encodes no other HCV protein.

2. An HCV vaccine as claimed in claim 1 , wherein polynucleotide encodes a core protein which is truncated from the carboxy terminal end in a sufficient amount to reduce the inhibitory effect of Core upon the expression of other HCV proteins

3. An HCV vaccine as claimed in 3 wherein the truncated core protein has a deletion of at least the C-terminal 10 amino acids.

4. An HCV vaccine as claimed in claim 3 wherein the truncated core protein consists of the Core 1-151 sequence.

5. An HCV vaccine as claimed in claim 3 wherein the truncated core protein consists of the Core 1-165 sequence.

6. An HCV vaccine as claimed in claim 1 , wherein the HCV proteins are present in the form of a fusion protein containing one or more of the HCV proteins.

7. An HCV vaccine as claimed in claim 6, wherein the fusion protein is a double fusion consisting of the polypeptide sequences of NS4B and NS5B.

8. An HCV vaccine as claimed in claim 6, wherein the fusion protein is a double fusion consisting of the polypeptide sequences of NS3 and Core

9. An HCV vaccine as claimed in claim 1, wherein the HCV proteins are encoded by the polynucleotide in more than one expression cassettes.

10. An HCV vaccine as claimed in claim 9, wherein the expression cassette encoding the Core protein is in a cis location downstream of the expression cassette which encodes at least on of the other HCV proteins.

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11. An HCV vaccine as claimed in claim 10 wherein the expression cassette encoding the Core protein is downstream of an expression cassette which encodes the NS5B protein.

12. An HCV vaccine as claimed in claim 1, wherein at least one of the HCV proteins present are inactivated by mutation.

13. An HCV vaccine as claimed in claim 12, wherein the polynucleotide encodes a NS5B protein that comprises a mutation in motif A.

14. An HCV vaccine as claimed in claim 12, wherein the polynucleotide encodes a NS3 protein wherein the protease activity has been abrogated by mutation in any of the catalytic triad amino acids.

15. An HCV vaccine as claimed in claim 12, wherein the polynucleotide encodes a NS3 protein wherein the helicase activity has been abrogated by mutation in one or more of the helicase motifs I, II, III or IV.

16. An HCV vaccine as claimed in claim 12, wherein the polynucleotide encodes a NS4B protein comprising a truncation to remove the highly variable N-terminal region.

17. An HCV vaccine as claimed in any one of claims 1 to 16 wherein the polynucleotide vaccine encodes any one of the HCV combinations 1 to 19.

18. An HCV vaccine as claimed in claim 1, wherein the polynucleotide is a DNA sequence.

19. An HCV vaccine as claimed in claim 18 wherein the DNA sequence is in the form of a plasmid.

20. A vaccine as claimed in any one of claims 1 to 17 wherein the oligonucleotides are codon optimised for expression in mammalian cells.

21. A method of preventing or treating an HCV infection in a mammal comprising administering a vaccine as claimed in any one of claims 1 to 17 to a mammal.

22. A method of vaccination of an individual comprising taking a polynucleotide vaccine as claimed in any one of claims 1 to 17, coating the polynucleotide onto gold beads and delivering the gold beads into the skin.

23. Use of an HCV vaccine as claimed in any one of claims 1 to 17 in the manufacture of a medicament for the treatment of HCV.